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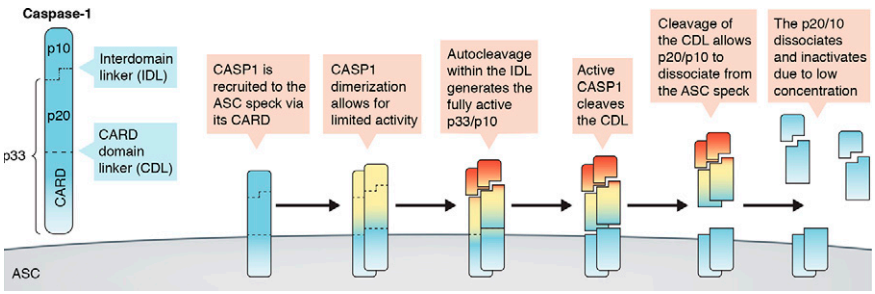
Defusing inflammasomes

In this issue of JEM, Boucher et al. (https://doi.org/10.1084/jem.20172222) report isolation of active caspase-1 from macrophages after inflammasome activation. Surprisingly, they find that caspase-1 is quickly inactivated upon autoproteolytic processing.

Insight from Andrew Sandstrom and Russell E. Vance

Inflammasomes are multiprotein complexes that recognize pathogens or noxious stimuli and initiate inflammatory immune responses via the recruitment and activation of the cytosolic protease caspase-1 (Rathinam and Fitzgerald, 2016). Active caspase-1 cleaves pro–IL-1β and pro–IL-18 to their functional isoforms. In addition, active caspase-1 cleaves and activates a pore-forming protein, gasdermin D (GSDMD), to initiate a form of cell death known as pyroptosis (Kayagaki et al., 2015; Shi et al., 2015). Although the process of inflammasome activation has been the subject of intense investigation, the mechanisms by which inflammasome responses are terminated are relatively poorly understood. The group of Kate Schroder and colleagues (see Boucher et al. in this issue) now report an unexpected mechanism of inflammasome inactivation that provides new insights into how pyroptosis and cytokine release may be differentially controlled in cells.

Caspase-1 is recruited to inflammasomes via its caspase activation and recruitment domain (CARD). The caspase-1 CARD can bind directly to inflammasome scaffold proteins that contain their own CARD or indirectly via the adaptor apoptosis-associated speck-like protein containing a CARD (ASC). Upon recruitment to inflammasomes, ASC polymerizes into a large filamentous structure called a speck. Recruitment of caspase-1 to the ASC speck leads to caspase-1 dimerization, autolytic cleavage between the caspase-1 CARD domain and the large (p20) subunit, and/or between the large and small (p10) subunits (see figure). These cleavage events ultimately generate a p20/p10 tetramer (dimer of the p20/p10 dimer) that has long been presumed to be the primary active enzyme. However, although processing of caspase-1 to the p20/p10 isoform is commonly observed after inflammasome activation, processing is not strictly required for capase-1 activity, which instead depends primarily on caspase-1 dimerization. In the absence of ASC, inflammasomes with their own CARDs can dimerize caspase-1 into an active but unprocessed form that can still initiate pyroptosis, presumably by GSDMD cleavage (Broz et al., 2010). Caspase-1 autoprocessing is a further step that depends on ASC and is required for optimal caspase-1–dependent cleavage of pro–IL-1β. However, the active form of caspase-1 in cells, and its fate after inflammasome activation, has largely been unexplored.



Pathway of caspase-1 activation and inactivation by autolytic cleavage. Caspase-1 (blue) is recruited to the ASC speck (gray). Dimerization of caspase-1 leads to limited activity (as indicated in yellow) and autolytic cleavage of the interdomain linker between the p20 and p10 subunits. The processed p33/p10 dimer complex is fully active (as indicated in red); however, further processing of the CARD domain linker leads to dissociation of caspase-1 from the ASC speck and inactivity because of low concentration.

To isolate active caspase-1 in cells after inflammasome activation, Boucher et al. (2018) used a biotinylated caspase probe that binds covalently to active caspase-1 enzyme. Surprisingly, the caspase-1 isoform that bound the probe was not the expected p20/p10 isoform, but was instead a partially processed p33/p10 isoform. Furthermore, the authors showed that formation of p20/p10 by cleavage within the CARD linker (CDL) resulted in the rapid inactivation of caspase-1. Inactivation appears to occur because caspase-1 p20/p10 tetramers rapidly dissociate once they are liberated from the ASC speck and diluted into the cytosol. An important implication of these results is that active caspase-1 is selectively found locally concentrated within inflammasome–ASC complexes. To support their findings, the authors mutated the CDL of Caspase-1 to prevent p20 formation. As predicted by their new model, CDL mutation resulted in a caspase-1 enzyme with enhanced and stabilized activity.

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Thus, autolytic processing of caspase-1 is a key step both in the activation—but also in the eventual inactivation—of caspase-1. From these results, the authors propose that caspase-1 activity acts as its own molecular timer to both activate and inactivate the protein after dimerization.

Boucher et al. (2018) further explore the role of ASC speck formation in caspase-1 activity. Comparing $Asc^{+/+}$ cells with $Asc^{+/-}$ cells that form smaller ASC specks, they note that larger ASC specks correlate with increased caspase-1 activation, but also with much faster turnover of caspase-1 into the fully processed inactive p20 fragment. Smaller ASC specks induce weaker caspase-1 activation, but the duration of caspase-1 activity is increased. These results are recapitulated when comparing NLRC4 inflammasome activation in $Asc^{+/+}$ versus $Asc^{-/-}$ cells (in which caspase-1 can still be activated via direct recruitment to the CARDs of NLRC4). In the $Asc^{-/-}$ cells, the majority of active caspase-1 is the full-length unprocessed isoform, and the duration of caspase-1 activity is greatly increased as compared with $Asc^{+/+}$ cells. As such, these results reveal a potential mechanism through which both the duration and intensity of caspase-1 activity is controlled.

In cell types such as macrophages that undergo rapid pyroptosis after inflammasome activation, cell death itself may still be the simplest mechanism by which inflammasome activity is terminated. However, certain cell populations, such as neutrophils, dendritic cells, and human monocytes, have been reported under certain scenarios to release processed IL-1β with minimal cell death (Chen et al., 2014; Zanoni et al., 2016; Gaidt and Hornung, 2017). In these scenarios, which seem to share weak inflammasome activation as a commonality, the inactivation mechanism proposed by Boucher et al. (2018) may be of particular importance: weak inflammasome activation may induce a low level of caspase-1 activity over a significant duration. These altered kinetics may allow cells to release processed cytokines without necessarily accumulating enough processed GSDMD to undergo pyroptosis. Slower caspase-1 activation kinetics may also allow the cell time to repair the membrane damage induced by the GSDMD pore. In contrast, classical and potent inflammasome activators, such as nigericin-induced activation of NLRP3 in macrophages, will induce a strong burst of caspase-1 activity, quickly followed by caspase-1 inactivation through pyroptosis and/or self-processing.

There are undoubtedly additional important implications of the new model of inflammasome inactivation proposed by Boucher et al. (2018). For example, a previous study had suggested that ASC specks could be released into the extracellular space and even transmitted between cells (Franklin et al., 2014). It may be interesting to consider how this process would be affected by the kinetics of caspase-1 activation/inactivation. In addition, there may be interesting implications for the development of therapeutics that target inflammasome or ASC assembly. According to the new results, an inhibitor that results in smaller speck formation may result in an undesirable prolongation of IL-1β processing and release. It will also be of interest to determine the relative importance, in different physiological scenarios, of caspase-1 inactivation via autoprocessing as compared with other mechanisms of inactivation, such as cell death or oxidation (Meissner et al., 2008). Regardless, the results of Boucher et al. (2018) demonstrate surprising dynamics in caspase-1 activity and raise novel questions about the temporal regulation of caspase-1.

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